Open-Source Quantitative Modeling of Tuberculosis Drug-Induced Cardiac Risks

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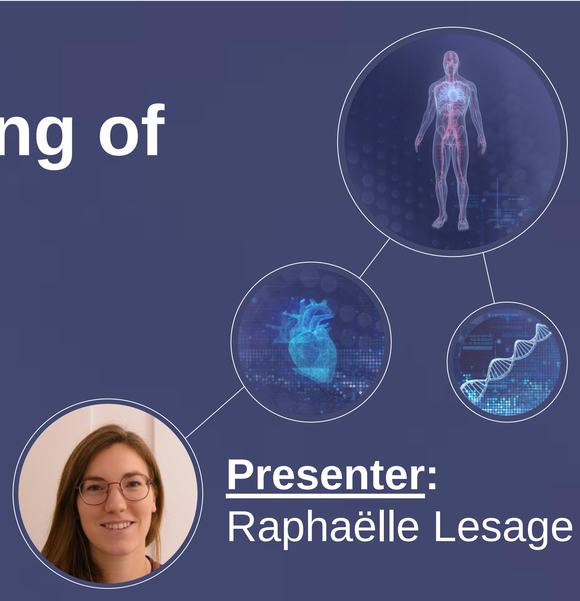

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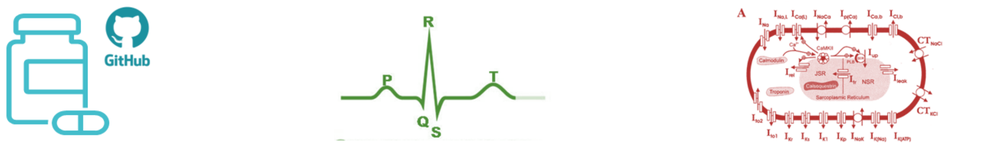
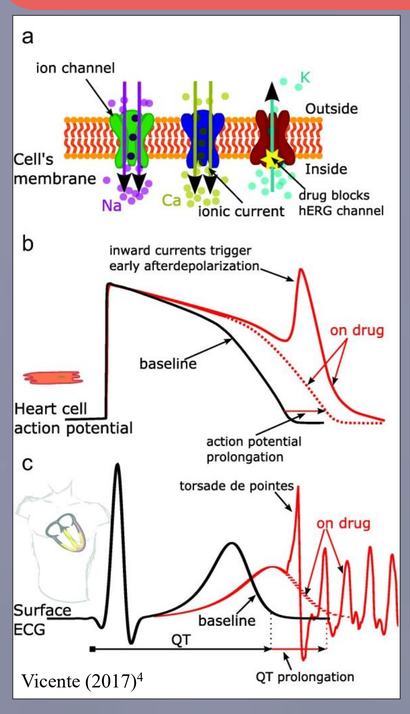
Intro

Some **anti-tuberculosis** (TB) drugs are associated with pro-arrhythmic risks[1]. In drug development, such a risk is assessed via the corrected QT (**QTc**) interval duration on the ECG. Drugs that Inhibit the cardiac ion channels may delay cardiac cells' **action potential** (**AP**), leading to QTc prolongation. The goals of this study were (1) to develop an **Open-Source QSP-PBPK** framework to predict the **cardiac risk of anti-TB drugs** and find **safe doses** (2) to ensure broader access to these technological advancements.

PBPK models – TB drugs | **Data-driven QTc model** | **Action potential model**



Methods



Anti-TB drug PBPK models were developed and made available in the latest OSPS v12.0[5], and validated with clinical data.

A data-driven QTc prolongation model was developed for Moxifloxacin and Bedaquilin, adapted from Gotta (2016)[2]. It utilizes *in vitro* ion channel (hERG) binding data to quantify how hERG inhibition translates to QTc prolongation.

Then, a mechanistic cardiac electrophysiology model[3] including population variability (male & female) was translated from MATLAB to R, validated against CiPA drugs, and applied to Bedaquilin ($IC_{50}^{hERG} = 1.6\mu M$). The input concentration was obtained from the PBPK model. Resulting drug effects on cardiomyocyte AP and duration at 90% repolarization (APD90) were computed.

Data-driven QTc prediction

Receptor binding

$$[LR] = \frac{[R_0] \times [L]}{K_i + [L]}$$

Ligand + Receptor → Bound Receptor

$[Drug]_{plasma_unbound}$ hERG channel

Fraction of blocked hERG channel

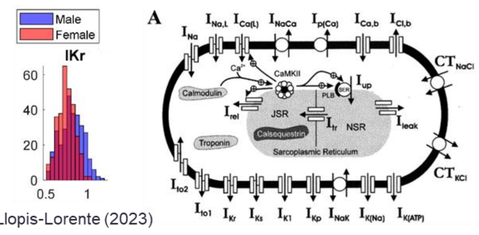
Transduction

$$E = \frac{E_m \cdot [LR]^Y}{LR_{50}^Y + [LR]^Y}$$

Bound Receptor → Effect

QTc prolongation ΔQTc

Mechanistic AP prediction



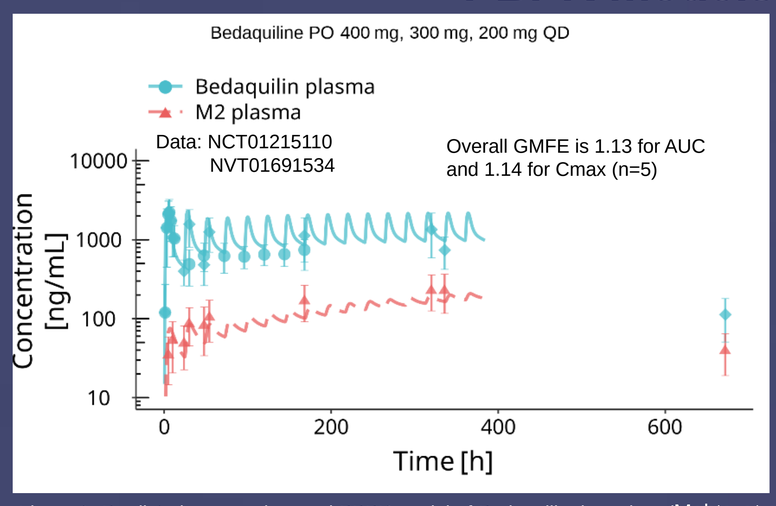
Results

- PBPK models of 5 anti-TB drugs replicated dose-concentration relationships (e.g., isoniazid evaluated across 11 clinical studies in healthy and TB patients). They were made available in OSPS v12.0 and will be uploaded on GitHub with reproducible evaluation reports.
- The data-driven QTc model predicts the dose-QTc relationship for Moxifloxacin at low doses and Bedaquilin metabolite at high doses
- The mechanistic AP model and the virtual population transferred to R successfully reproduce the effect of high-risk CiPA drugs on AP in male and female virtual populations.
- The model predicts no cardiac effect of Bedaquilin at therapeutic dose, but APD90 increases with higher unbound concentrations (e.g., in case of co-therapy/DDI): increases by 14% at 500nM.
- *In vitro* current inhibition measurements for TB drugs are necessary to improve forward predictions

Conclusion

PBPK models of TB drugs and QSP cardiac effect models have been implemented in an open-source framework to enhance dose testing and cardiac safety assessment in various populations. This ensures that technological advancements in anti-TB drug PK and PD are accessible to a broader audience. The next steps involve further testing and validating the framework with new *in vitro* data for TB drugs.

Transfer to OSPS v12 and validate anti-TB drugs PBPK models



PBPK models

GitHub

- Bedaquilin
- Rifampicine
- Isoniazid
- Moxidectine
- Moxifloxacine

GitHub PBPK library [6]

Figure 1: Predicted versus observed PBPK model of Bedaquilin, based on (Mehta *et al.*, 2024). Covers 3 studies with po admin. of Bedaquilin from 200 to 700 mg.

Data-driven QTc modelling

Receptor binding & hERG block potency model

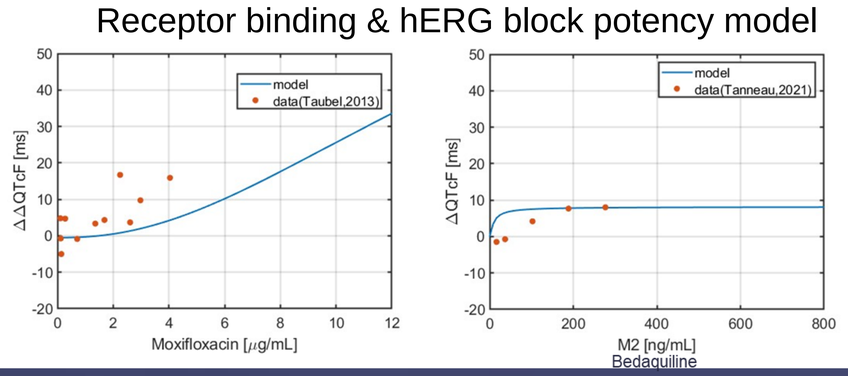


Figure 2: QTc prediction model predicts dose-QTc relationship for Moxifloxacin and Bedaquilin reported in thorough QT studies (Taubel, 2013 and Tanneau, 2021). Fridericia's correction was implemented using a resting heart rate of 75bpm. ΔQTcF for the placebo was assumed to be 0.5ms (reported as close to 0 in the literature).

Mechanistic AP model in R - Validation

CiPA drugs

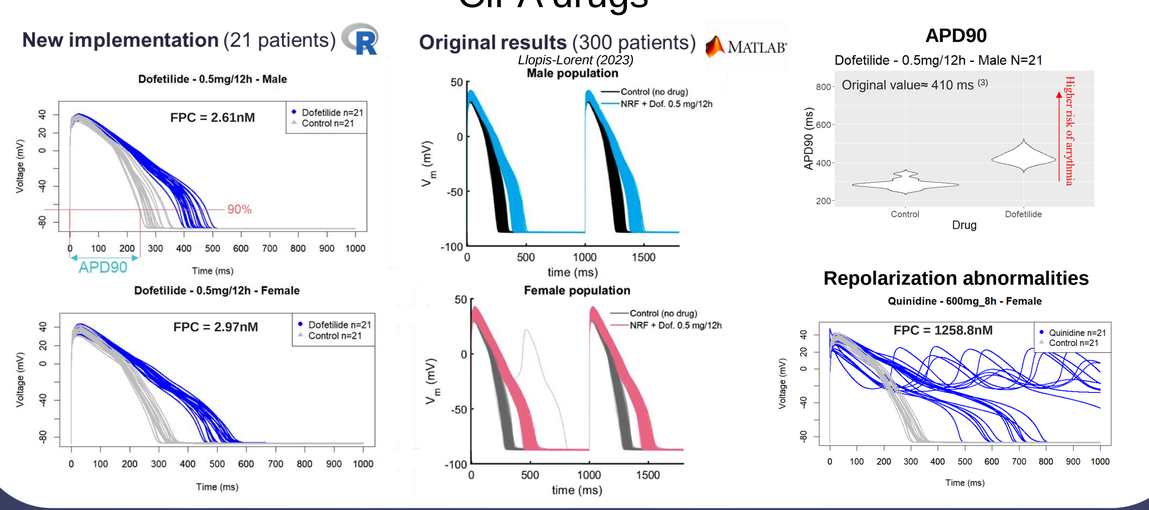
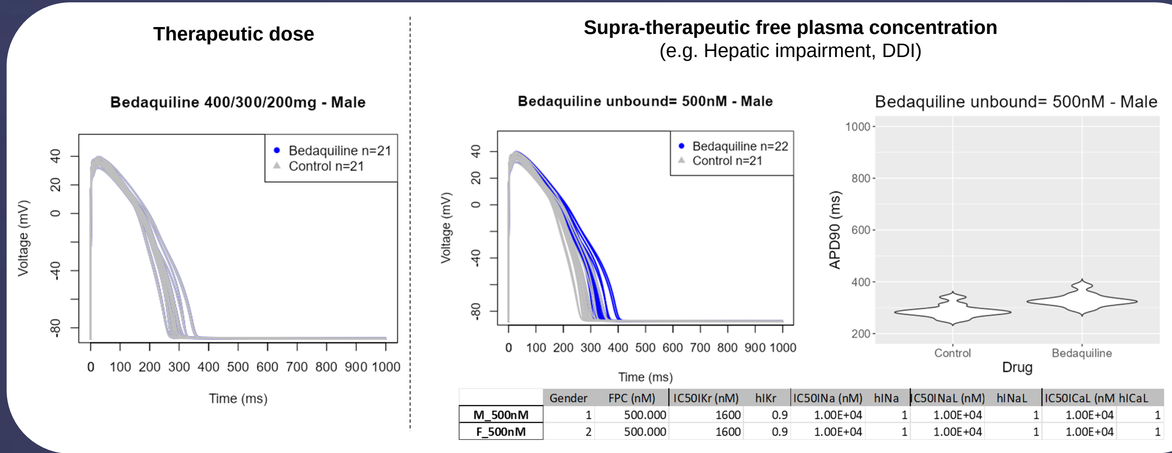


Figure 3: R implementation validation with benchmark CiPA drugs. AP predictions could be reproduced in R compared to the original paper. Dofetilide was modelled with $IC_{50}^{hERG} = 1.47nM, hKr = 0.63$ and high IC_{50} for other channels. 'FPC'= free plasma concentration. The APD90 in increased under Dofetilide, in line with known pro-arrhythmic risks. Expected repolarization abnormalities are also reproduced.

Cardiac effect of anti-TB drug Bedaquilin



	Gender	FPC (nM)	IC50IKr (nM)	hIKr	IC50INa (nM)	hINa	C50INaL (nM)	hINaL	IC50ICaL (nM	hICaL
M_500nM	1	500.000	1600	0.9	1.00E+04	1	1.00E+04	1	1.00E+04	1
F_500nM	2	500.000	1600	0.9	1.00E+04	1	1.00E+04	1	1.00E+04	1

Figure 4: Prediction of Bedaquilin's effect on the cardiomyocyte action potential. A therapeutic dose of 400mg followed by 300mg and weekly dosing of 200mg does not trigger AP delay. But free plasma concentration can be increased in case of hepatic impairment or drug-drug interaction during co-therapy (CYP3A4, CYP2C8/19). Unbound plasma concentration of 500nM increases APD90 by 14% in males.

References

[4] J. Brust. et al. (2021) Effectiveness and Cardiac Safety of Bedaquiline-Based Therapy for Drug-Resistant Tuberculosis: A Prospective Cohort Study.

[2] V. Gotta et al. (2016) Application of a systems pharmacology model for translational prediction of hERG-mediated QTc prolongation

[3] Llopis-Lorente (2023) Combining pharmacokinetic and electrophysiological models for early prediction of drug-induced arrhythmogenicity.

[4] J. Vincente (2017) Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the "CiPA" Initiative and Design of a Prospective Clinical Validation Study.

[5] Lippert J, et al. Open Systems Pharmacology community - an open access, open source, open science approach to modeling and simulation in pharmaceutical sciences. CPT Pharmacometrics Syst Pharmacol. 2019 Oct 31

[6] https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library

Modeling Scaling Coding

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